



How Berberine Improves the Impact of Sulforaphane

With Dr. John Gildea and Dr. Martin Katz

David Roberts:

Hey everybody. It's David Roberts and you are listening to the Mara Labs podcast. And today I have Dr. John Gildea and Dr. Martin Katz with me, and we are going to be talking about a molecule that's near and dear to our hearts called berberine. And berberine is not the most popular phytochemical out there, but it is one that has some amazing benefits that we want to highlight today. And one of the benefits is how it interacts with another molecule that we really like called sulforaphane. And John, why don't you dive in and explain how those two molecules interact together?

John Gildea:

So, I understand berberine probably best as how it interacts with Nrf2. Nrf2 is the target of sulforaphane. And just to go back and summarize a little bit of mechanism, sulforaphane goes into a cell, sulforaphane has amazing ability to go just about everywhere. It thrives in hydrophobic and hydrophilic environment. So it gets to its target really amazingly well. So it has that really on its side to go over the induction event that happens when you take sulforaphane is there's a complex in the cytoplasm of all cells in the body that is this Nrf2 complex and its basal state is to be degraded. So it's being degraded all the time and therefore it's not on, it's in an off state most of the time. And then sulforaphane interacts with these molecules, gets in between Nrf2 and keep one and causes it to be stabilized.

John Gildea:

So the mechanism of induction for sulforaphane is that it makes the amount of Nrf2 increase pretty dramatically. But the way that it functions, it has to go into the nucleus and turn on genes. And that's kind of where berberine comes into effect. Berberine makes the nuclear accumulation of Nrf2 increase. So that's how they work together is that sulforaphane increases the amount Nrf2 that accumulates in the cell, and berberine makes it accumulate more in the nucleus. And that's how they work together. A big part of the benefit for it, in my understanding, is through that induction. But I think there's a lot more to the mechanism of how berberine works and there are independent components of it, but my favorite component of berberine is its enhancement of Nrf2.

David Roberts:

And so how long will that interaction last?

John Gildea:

So berberine is a molecule that has a really complex bioavailability where it goes, how it's absorbed, how it's metabolized. So how long it gets to cells and turns things on, I think is still a big question but it does get to the nucleus. And I think the issue there is that when Nrf2 is induced, it has this tendency to turn its own self on and as well as change the epigenetics of the context of turning it on. So Nrf2 is a strange molecule on that it tends to stay on after it's induced. So you're wanting to get it over a hurdle where you get gene induction, then Nrf2 turns itself on and tends to stay on for longer than a typical transcription factor. So when you think about detox, you want it to stay on for a while in order to accomplish that ability to move toxins out of your body. So tends to stay on for a pretty long time even though the induction event is long gone.

David Roberts:

And I remember reading at least with the antioxidant response system in Nrf2, a 72 hour turn on, let's just back up too. And when you talk about epigenetics, you mentioned that word. Can you in layman's terms discuss what that is. We've mentioned it before, but just would be good to define that.

John Gildea:

At least the simple understanding of epigenetics is that the sequence of the genes that you are born with is your genetics and the epigenetics is how the expression of those genes change from day to day. Probably the best context would be how a lot of people understand exercise. And I think Martin probably will talk a little bit about those sort of factors, but berberine is similar to that. It's turning on a set of genes, but it's also changing your epigenome, what genes are on. And it tends to move them in the right direction, which is a really great thing.

David Roberts:

So Martin, do you use berberine in your clinic and if so, what benefits are you seeing?

Martin Katz:

It's interesting listening to John and just with as much success as berberine has in the literature and as much success as it's had for thousands of years and being used in treatment of conditions throughout, you would think that there would be more of an emphasis on berberine as sulforaphane. But these molecules, as John pointed out are very difficult to get into the system and very difficult to get to the point that it's making a bioavailable impact on your cell. And so maybe this is why these things are not more unknown. And if you look at berberine.

David Roberts:

What is the bioavailability? How much does get in through the gut barrier?

Martin Katz:

Like 0.5%. I mean, it is a very small amount.

David Roberts:

It's under 1%.

John Gildea:

And rats and humans have been studied and generally very low.

Martin Katz:

Very low. So again, this is possibly the reason, but if you look at the data on berberine, that's one of these molecules again, I certainly like the Nrf2. I love sulforaphane for so many reasons because it has a major impact on not only inflammation, but antioxidation, detox because of how it affects the nucleus and how it affects your genome and your epigenome and berberine similar. And I think it works in different ways than just sulforaphane alone. So, if you look at the studies and how it affects cholesterol, how it affects your blood sugar, how it affects your microbiome, these studies are pretty profound. And so you betcha I'm using it in the clinic to help my patients out, because as much of an impact as we've made with regard to technology and the things we can offer patients with regard to medications and these incredible procedures, we're still seeing an amazing amount of cardiovascular problems.

Martin Katz:

And so if there's things that you can do to impact a person's risk of some of those problems, then you definitely want to have that in your clinical practice and a tool to help your patients out with regard to

inflammation and oxidation and again, the microbiome. So berberine is a very impressive molecule, great support of sulforaphane. And I, again, kind of liken it, Jeffrey Smith, we've been on a podcast with him and he likens sulforaphane and certainly berberine and again, how they work together. If you go to war, you don't want to just bring in the coast guard or the army or the Marines. You want to have firepower. You want to have troops on the ground. You want to have intelligence, you want to have all of these things. If you're just sending one molecule like current medicines work, they're very targeted at one thing.

Martin Katz:

And we've realized that oftentimes it's not just one thing that drives a process, it's numerous things. And the way sulforaphane works, the way berberine works, you're creating a massive response to a lot of these processes. Again, another way to look at it, if you have a basketball team and you have a bunch of five foot eight point guards going up against a team that has a 6'10"s, seven foot two front man, you may win the team if you're shooting lights out on three pointers, but there's a good chance you're going to lose to a team that's got really good ball handlers and good guys in the paint. Or soccer, if you just have defense men no goalie, you can look at it numerous different ways, but if you're putting out a bunch of people who know what they're doing all over the field, you got a much better chance of succeeding. And that's the way I look at berberine and sulforaphane.

David Roberts:

So Martin, you mentioned cholesterol, how berberine impacts cholesterol in a good way. We'll have a link in the show notes to a paper or papers on that. You mentioned berberine and its impact on blood glucose levels. That's interesting because most of the lit, well, all of the literature currently, you need to take berberine for weeks to months to see that impact on blood glucose. And the exciting thing with our form of berberine called BerbElite is that you can see the benefit on blood glucose. John, you did the study, was it hours?

John Gildea:

Yeah (affirmative). Hours.

David Roberts:

So not months, not weeks, hours. So that speaks to the bioavailability. I believe in that the currently what's available on the market in the regular berberine, because it's under 1% gets in through the gut barrier into your circular system. It takes a while, along while to see those benefits. Whereas our form gets in pretty quickly, very quickly. It impacts the situation quickly as well. But we'll have a link also in the show notes to a little preclinical study we did on blood sugar and really our impact in what we're interested in is how to get into [inaudible] quickly when you're on the ketogenic diet. And then Martin, you mentioned microbiome. I haven't done the readings on microbiome and berberine, what's out there? How does berberine impact the microbiome?

Martin Katz:

Well, I mean, it's been used for thousands of years in Chinese medicine to treat diarrhea symptom. And so if you look at the way it helps dysbiosis in the gut and really affect a positive microbiome there's studies there. And again, you look at the way sulforaphane works and again, you're going to see these things working well together.

David Roberts:

Great. John, can you just give us, you take a capsule of berberine? What happens?

John Gildea:

It's a complicated metabolism for sure. What Martin just says, super interesting. I don't think I really connected it before was that it's ancient Chinese and probably [inaudible] origin is mostly contained within the intestines. And so, lack of bioavailability, it's doing all that great stuff without getting into your blood system. So that's cool that matches, but there's a whole different level of benefit you can get if you can get it into your bloodstream. So the metabolism of berberine is complex, for sure. I'm pretty sure that it does get into the hepatic portal system. And so most of the resident levels of berberine is back and forth from the liver and the intestines, a component of the microbiome converts it to dihydroberberine, which makes it more soluble.

John Gildea:

And that's one of the big hurdles of berberine is that it's just not even soluble. So what does get soluble? And it won't even get to the cells that are lining the intestine, unless it's made soluble. You have these big rocks floating by in the small intestine and they're doing very little. Until the microbiome acts on it and makes it soluble so it can get to the cells. So, that does happen. And I think the really interesting thing there is that it has such big effects even without being bioavailable. But if you can get berberine intact past the [inaudible] and into the circulation then you can mimic a lot of the in-vitro studies that are done with berberine. Where in cell culture conditions, you don't have that big barrier. So you see these big effects with berberine at relatively low concentrations and it's hard to achieve that level of berberine, unless you can bypass the [inaudible] . Because frankly, they like to pump it back into your intestines better than they like to let it go past.

John Gildea:

So even if you get some into your circulatory system, it's pumping it back into the intestines. So, definitely, there's some hurdles there to get it bioavailable and we're pretty happy that we can get it past the [inaudible] .

David Roberts:

Another benefit that we won't go into depth on here, but as you're listening to this, can do your own research is looking at PubMed at this pathway called c-MYC, C-M-Y-C, and how it's impacted by berberine. We definitely can't talk about different disease states. And so we'll just leave it at that for you to do your own research in what's out there in the literature. But John, you also mentioned before we hit record about a paper you read with oxytocin.

John Gildea:

Very interesting. I love that topic because it happens to be a really favorite paper of mine that involves epigenetics, a topic that I'm really interested in. And it's a model system of hypertension, where they give corticosteroids to a mother and this isn't a mouse model. And those pups that grow up when they reach middle age, they are assault sensitive hypertensive. And so that's a long time and generation of these mice. And what's interesting is that if when they're pups, they have an interaction with their moms. I feel like they have very close interaction, oxytocin is secreted. It's the, I guess you could call it, love hormone.

John Gildea:

So when you meet eyes with your mom and you have that loving feeling, oxytocin is released. It's also what causes milk let down. I think that's right. And so if they have a prolonged time with their mother in that way, you can counteract that effect. If you wean them very early, it's worse. And then you can mimic by just injecting oxytocin. So that feeling of love and connectedness is through this hormone called oxytocin. So it's generally a good feeling, satisfied feeling. And so berberine is known to induce oxytocin. And so it's added benefit to berberine that a lot of people don't focus on.

David Roberts:

Can we get that paper to put in the show notes as well?

John Gildea:

Sure.

David Roberts:

And we'll also have the link to a podcast that John and Martin did looking at how berberine increases both serotonin and dopamine. In fact, the title of the paper they reviewed was comparing berberine to Valium and how berberine out performed Valium as a sleep aid. So look in the show notes and we're going to leave it there for today. Gentlemen, thank you for joining us on this. And we'll be back with another episode next week, the Mara Labs podcast. Thanks so much.

John Gildea:

Thank you. Take care of [inaudible].

David Roberts:

Awesome.